WEST Search History

DATE: Wednesday, August 06, 2003

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=OR		
L11	L10 and (identif$7 or determin$7 or detect$7) with receptor with ligand	119	L11
L10	L6 and receptor with ligand	323	L10
L9	L7 and high-throughput	0	L9
L8	L6 and (cell with microtiter).clm.	3	L8
L7	L6 and cell with immobil$6	171	L7
L6	L5 and (identif$5 or determin$5 or detect$6) with (ligand or bind$3)	1053	L6
L5	L1 and @py<1998	2387	L5
L4	L3 not ay>1998	0	L4
L3	cell same microtiter	9773	L3
L2	L1 and (identif$5 or determin$5 or detect$6) with (ligand or bind$3)	3424	L2
L1	cell with microtiter	6328	L1

END OF SEARCH HISTORY

STN Search History

FILE 'HOME' ENTERED AT 07:45:41 ON 06 AUG 2003

L1 330 (BRUTON## (A) TYROSINE (A) KINASE OR BTK (S) KINASE) AND (MEMBRA NE OR SURFACE)

L5 32 L4 AND (BRUTON## (A) TYROSINE (A) KINASE OR BTK (S) KINASE) (P) (MEMBRANE OR SURFACE)

L6 14 L5 AND (TYROSINE (A) KINASE OR GROWTH (A) FACTOR) (S) RECEPTOR

L7 30 L3 AND (BRUTON## (A) TYROSINE (A) KINASE OR BTK) (S) (MEMBRANE OR SURFACE)

L8 9 L7 AND (TYROSINE (A) KINASE OR GROWTH (A) FACTOR) (S) RECEPTOR

(FILE 'HOME' ENTERED AT 07:45:41 ON 06 AUG 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS' ENTERED AT 07:46:06 ON 06 AUG 2003

L1 330 S (BRUTON## (A) TYROSINE (A) KINASE OR BTK (S) KINASE) AND (MEM
L2 167 DUP REM L1 (163 DUPLICATES REMOVED)
L3 80 S L2 NOT PY>1998
L4 54 S L3 AND (RECEPTOR OR G-PROTEIN OR G (A) PROTEIN)
L5 32 S L4 AND (BRUTON## (A) TYROSINE (A) KINASE OR BTK (S) KINASE)
L6 14 S L5 AND (TYROSINE (A) KINASE OR GROWTH (A) FACTOR) (S) RECEPT
L7 30 S L3 AND (BRUTON## (A) TYROSINE (A) KINASE OR BTK) (S) (MEMBR
L8 9 S L7 AND (TYROSINE (A) KINASE OR GROWTH (A) FACTOR) (S) RECEPT
L9 0 S L8 NOT L6

L6 ANSWER 1 OF 14 MEDLINE on STN
AN 1998190079 MEDLINE
DN 98190079 PubMed ID: 9524120
TI **Btk**/Tec **kinases** regulate sustained increases in intracellular Ca2+ following B-cell **receptor** activation.
AU Fluckiger A C; Li Z; Kato R M; Wahl M I; Ochs H D; Longnecker R; Kinet J P; Witte O N; Scharenberg A M; Rawlings D J
CS Department of Microbiology and Molecular Genetics, University of California at Los Angeles, Los Angeles, CA 90095-1662, USA.
NC AR01912 (NIAMS)
CA12800 (NCI)
GM0823 (NIGMS)
+
SO EMBO JOURNAL, (1998 Apr 1) 17 (7) 1973-85.
Journal code: 8208664. ISSN: 0261-4189.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199806
ED Entered STN: 19980611
Last Updated on STN: 19980611
Entered Medline: 19980601
AB Bruton's **tyrosine kinase** (**Btk**) is essential for B-lineage development and represents an emerging family of non-**receptor tyrosine kinases** implicated in signal transduction events initiated by a range of cell **surface receptors**. Increased dosage of Btk in normal B cells resulted in a striking enhancement of extracellular calcium influx following B-cell antigen **receptor** (BCR) cross-linking. Ectopic expression of **Btk**, or related **Btk**/Tec family **kinases**, restored deficient extracellular Ca2+ influx in a series of novel **Btk**-deficient human B-cell lines. Btk and phospholipase Cgamma (PLCgamma) co-expression resulted in tyrosine phosphorylation of PLCgamma and required the same Btk domains as those for Btk-dependent calcium influx. **Receptor**-dependent Btk activation led to enhanced peak inositol trisphosphate (IP3) generation and depletion of thapsigargin (Tg)-sensitive intracellular calcium stores. These results suggest that Btk maintains increased intracellular calcium levels by controlling a Tg-sensitive, IP3-gated calcium store(s) that regulates store-operated calcium entry. Overexpression of dominant-negative Syk dramatically reduced the initial phase calcium response, demonstrating that **Btk** /Tec and Syk family **kinases** may exert distinct effects on calcium signaling. Finally, co-cross-linking of the BCR and the inhibitory **receptor**, FcgammaRIIb1, completely abrogated Btk-dependent IP3 production and calcium store depletion. Together, these data demonstrate that Btk functions at a critical crossroads in the events controlling calcium signaling by regulating peak IP3 levels and calcium store depletion.

L6 ANSWER 2 OF 14 MEDLINE on STN
AN 1998184817 MEDLINE
DN 98184817 PubMed ID: 9516410
TI **Receptor** docking sites for **G-protein** betagamma subunits. Implications for signal regulation.
AU Wu G; Benovic J L; Hildebrandt J D; Lanier S M
CS Department of Pharmacology, Medical University of South Carolina, Charleston, South Carolina 29425, USA.
NC DK37219 (NIDDK)
GM47417 (NIGMS)

NS24821 (NINDS)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Mar 27) 273 (13) 7197-200.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199804
ED Entered STN: 19980430
Last Updated on STN: 20000303
Entered Medline: 19980423
AB We report the direct interaction of Gbetagamma with the third intracellular (i3) loop of the M2- and M3-muscarinic **receptors** (MR) and the importance of this interaction relative to effective phosphorylation of the **receptor** subdomain. The i3 loop of the M2- and the M3-MR were expressed in bacteria and purified as glutathione S-transferase fusion proteins for utilization as an affinity matrix and to generate substrate for **receptor** subdomain phosphorylation. In its inactive heterotrimeric state stabilized by GDP, brain **G-protein** did not associate with the i3 peptide affinity matrix. However, stimulation of subunit dissociation by GTPgammaS/Mg2+ resulted in the retention of Gbetagamma, but not the Galpha subunit, by the M2- and M3-MR i3 peptide resin. Purified Gbetagamma bound to the M3-MR i3 peptide with an apparent affinity similar to that observed for the Gbetagamma binding domain of the **receptor** kinase GRK2 and **Bruton tyrosine kinase**, whereas transducin betagamma was not recognized by the M3-MR i3 peptide. Effective phosphorylation of the M3-MR peptide by GRK2 required both Gbetagamma and lipid as is the case for the intact **receptor**. Incubation of purified GRK2 with the i3 peptide in the presence of Gbetagamma resulted in the formation of a functional ternary complex in which Gbetagamma served as an adapter protein. Such a complex provides a mechanism for specific spatial translocation of GRK2 within the cell positioning the enzyme on its substrate, the activated **receptor**. The apparent ability of Gbetagamma to act as a docking protein may also serve to provide an interface for this class of **membrane**-bound **receptors** to an expanded array of signaling pathways.

L6 ANSWER 5 OF 14 MEDLINE on STN
AN 97449377 MEDLINE
DN 97449377 PubMed ID: 9305846
TI Direct stimulation of Bruton's tyrosine kinase by G(q)-protein alpha-subunit.
AU Bence K; Ma W; Kozasa T; Huang X Y
CS Department of Physiology, Cornell University Medical College, New York 10021, USA.
SO NATURE, (1997 Sep 18) 389 (6648) 296-9.
Journal code: 0410462. ISSN: 0028-0836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709
ED Entered STN: 19971013
Last Updated on STN: 20000303
Entered Medline: 19970930
AB Heterotrimeric guanine-nucleotide-binding regulatory **proteins** (**G proteins**) transduce signals from a wide variety of cell-**surface receptors** to generate physiological responses. Protein-tyrosine kinases are another group of critical

cellular signal transducers and their malfunction often leads to cancer. Although activation of **G-protein**-coupled **receptors** can elicit rapid stimulation of cellular protein-tyrosine phosphorylation, the mechanism used by **G proteins** to activate protein-**tyrosine kinases** is unclear. Here we show that the purified alpha-subunit of the G(q) class of **G proteins** (**G**[alpha]q) directly stimulates the activity of a purified non-**receptor kinase**, Bruton's **tyrosine kinase** (**Btk**), whereas purified alpha-subunits from G(il), G(O) or G(z) proteins do not. G(alpha)q can also activate Btk in vivo. Furthermore, in **Btk**-deficient cells, stimulation of another **kinase**, a p38 MAP **kinase**, by Gq-coupled **receptors** is blocked. Our results demonstrate that certain protein-tyrosine kinases can be direct effectors of **G proteins**.

L6 ANSWER 6 OF 14 MEDLINE on STN
AN 96251295 MEDLINE
DN 96251295 PubMed ID: 8668162
TI Regulation of **Btk** by Src family tyrosine **kinases**.
AU Afar D E; Park H; Howell B W; Rawlings D J; Cooper J; Witte O N
CS Department of Microbiology, Howard Hughes Medical Institute, University of California--Los Angeles, 90095-1662, USA.
NC CA12800 (NCI)
CA41072 (NCI)
R019102
SO MOLECULAR AND CELLULAR BIOLOGY, (1996 Jul) 16 (7) 3465-71.
Journal code: 8109087. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199608
ED Entered STN: 19960819
Last Updated on STN: 19960819
Entered Medline: 19960808
AB Loss of function of Bruton's **tyrosine kinase** (**Btk**) results in X-linked immunodeficiencies characterized by a broad spectrum of signaling defects, including those dependent on Src family **kinase**-linked cell **surface receptors**. A gain-of-function mutant, Btk*, induces the growth of fibroblasts in soft agar and relieves the interleukin-5 dependence of a pre-B-cell line. To genetically define **Btk** signaling pathways, we used a strategy to either activate or inactivate Src family **kinases** in fibroblasts that express **Btk***. The transformation potential of Btk* was dramatically increased by coexpression with a partly activated c-Src mutant (E-378 --> G). This synergy was further potentiated by deletion of the Btk Src homology 3 domain. Downregulation of Src family **kinases** by the C-terminal Src **kinase** (Csk) suppressed **Btk*** activation and biological potency. In contrast, **kinase**-inactive Csk (K-222 --> R), which functioned as a dominant negative molecule, synergized with **Btk*** in biological transformation. Activation of Btk* correlated with increased phosphotyrosine on transphosphorylation and autophosphorylation sites. These findings suggest that the Src and **Btk kinase** families form specific signaling units in tissues in which both are expressed.

L6 ANSWER 7 OF 14 MEDLINE on STN
AN 96223940 MEDLINE
DN 96223940 PubMed ID: 8629002

TI Activation of **BTK** by a phosphorylation mechanism initiated by SRC family **kinases**.
AU Rawlings D J; Scharenberg A M; Park H; Wahl M I; Lin S; Kato R M; Fluckiger A C; Witte O N; Kinet J P
CS Department of Microbiology and Molecular Genetics, University of California, Los Angeles 90095-1662, USA.
NC AR01912 (NIAMS)
AR36834 (NIAMS)
CA09120-20 (NCI)
+
SO SCIENCE, (1996 Feb 9) 271 (5250) 822-5.
Journal code: 0404511. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199606
ED Entered STN: 19960708
Last Updated on STN: 20000303
Entered Medline: 19960625
AB Bruton's **tyrosine kinase** (**BTK**) is pivotal in B cell activation and development through its participation in the signaling pathways of multiple hematopoietic **receptors**. The mechanisms controlling **BTK** activation were studied here by examination of the biochemical consequences of an interaction between **BTK** and SRC family **kinases**. This interaction of **BTK** with SRC **kinases** transphosphorylated **BTK** on tyrosine at residue 551, which led to **BTK** activation. BTK then autophosphorylated at a second site. The same two sites were phosphorylated upon B cell antigen **receptor** cross-linking. The activated **BTK** was predominantly **membrane**-associated, which suggests that **BTK** integrates distinct **receptor** signals resulting in SRC **kinase** activation and **BTK** **membrane** targeting.

L6 ANSWER 9 OF 14 MEDLINE on STN
AN 96009555 MEDLINE
DN 96009555 PubMed ID: 7565679
TI Src family protein tyrosine kinases induce autoactivation of Bruton's tyrosine kinase.
AU Mahajan S; Fargnoli J; Burkhardt A L; Kut S A; Saouaf S J; Bolen J B
CS Department of Oncology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543, USA.
SO MOLECULAR AND CELLULAR BIOLOGY, (1995 Oct) 15 (10) 5304-11.
Journal code: 8109087. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199510
ED Entered STN: 19951227
Last Updated on STN: 19951227
Entered Medline: 19951025
AB Bruton's **tyrosine kinase** (**Btk**) is tyrosine phosphorylated and enzymatically activated following ligation of the B-cell antigen **receptor**. These events are temporally regulated, and **Btk** activation follows that of various members of the Src family of protein tyrosine **kinases**, thus raising the possibility that Src **kinases** participate in the **Btk** activation process. We have evaluated the mechanism underlying **Btk** enzyme

activation and have explored the potential regulatory relationship between **Btk** and Src protein **kinases**. We demonstrate in COS transient-expression assays that Btk can be activated through intramolecular autophosphorylation at tyrosine 551 and that Btk autophosphorylation is required for Btk catalytic functions. Coexpression of **Btk** with members of the Src family of protein tyrosine **kinases**, but not Syk, led to **Btk** tyrosine phosphorylation and activation. Using a series of point mutations in Blk (a representative Src protein **kinase**) and **Btk**, we show that Src **kinases** activate **Btk** through an indirect mechanism that requires **membrane** association of the Src enzymes as well as functional **Btk** SH3 and SH2 domains. Our results are compatible with the idea that Src protein tyrosine **kinases** contribute to **Btk** activation by indirectly stimulating **Btk** intramolecular autophosphorylation.

L6 ANSWER 10 OF 14 MEDLINE on STN
AN 95023944 MEDLINE
DN 95023944 PubMed ID: 7524079
TI Temporal differences in the activation of three classes of non-transmembrane protein **tyrosine kinases** following B-cell antigen **receptor surface** engagement.
AU Saouaf S J; Mahajan S; Rowley R B; Kut S A; Fargnoli J; Burkhardt A L; Tsukada S; Witte O N; Bolen J B
CS Department of Molecular Biology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Sep 27) 91 (20) 9524-8.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199410
ED Entered STN: 19941222
Last Updated on STN: 19970203
Entered Medline: 19941027
AB We evaluated in WEHI 231 B cells the time-dependent responses of Lyn, Blk, **Btk**, Syk, and three members of the Jak family of protein **tyrosine kinases** following antibody-mediated **surface** engagement of the B-cell antigen **receptor**. Our results show that the enzyme activities of Lyn and Blk were stimulated within seconds of antigen **receptor** engagement and correlated with the initial tyrosine phosphorylation of the Ig alpha and Ig beta subunits of the B-cell antigen **receptor**. Btk enzyme activity was also transiently stimulated and was maximal at approximately 5 min after B-cell **receptor surface** binding. Syk activity gradually increased to a maximum at 10-30 min following **receptor** ligation and was found to parallel the association of Syk with the tyrosine phosphorylated Ig alpha and Ig beta subunits of the **receptor**. While the specific activities of the Jak1, Jak2, and Tyk2 protein **tyrosine kinases** were unaltered following B-cell **receptor** ligation, the abundance of Jak1 and Jak2 were increased 3- to 4-fold within 10 min of **receptor** engagement. These results demonstrate that multiple families of non-transmembrane protein **tyrosine kinases** are temporally regulated during the process of B-cell antigen **receptor**-initiated intracellular signal transductio

L8 ANSWER 3 OF 9 MEDLINE on STN
AN 96223940 MEDLINE
DN 96223940 PubMed ID: 8629002
TI Activation of **BTK** by a phosphorylation mechanism initiated by SRC family **kinases**.
AU Rawlings D J; Scharenberg A M; Park H; Wahl M I; Lin S; Kato R M; Fluckiger A C; Witte O N; Kinet J P
CS Department of Microbiology and Molecular Genetics, University of California, Los Angeles 90095-1662, USA.
NC AR01912 (NIAMS)
AR36834 (NIAMS)
CA09120-20 (NCI)
+
SO SCIENCE, (1996 Feb 9) 271 (5250) 822-5.
Journal code: 0404511. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199606
ED Entered STN: 19960708
Last Updated on STN: 20000303
Entered Medline: 19960625
AB Bruton's **tyrosine kinase** (**BTK**) is pivotal in B cell activation and development through its participation in the signaling pathways of multiple hematopoietic **receptors**. The mechanisms controlling **BTK** activation were studied here by examination of the biochemical consequences of an interaction between **BTK** and SRC family **kinases**. This interaction of **BTK** with SRC **kinases** transphosphorylated **BTK** on tyrosine at residue 551, which led to **BTK** activation. BTK then autophosphorylated at a second site. The same two sites were phosphorylated upon B cell antigen receptor cross-linking. The activated **BTK** was predominantly **membrane**-associated, which suggests that **BTK** integrates distinct receptor signals resulting in SRC **kinase** activation and **BTK membrane** targeting.

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